Exhibit 22

New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58942 (Dec. 11, 1992)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 601

[Docket No. 91N–0278]

RIN 0905–AD66

New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing final regulations under which the agency will accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provisions for any necessary continued study of the drugs' clinical benefits after approval or with restrictions on use, if necessary. These new procedures are intended to provide expedited marketing of drugs for patients suffering from such illnesses when the drugs provide meaningful therapeutic benefit compared to existing treatment. Accelerated approval will be considered in two situations: (1) When approval can be reliably based on evidence from adequate and well-controlled studies of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity, pending completion of studies to establish and define the degree of clinical benefits to patients; and (2) when FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted. Drugs or biological products approved under these procedures will have met the requisite standards for safety and effectiveness under the Federal Food, Drug, and Cosmetic Act (the act) or the Public Health Service Act (the PHS Act) and, thus, will have full approval for marketing.

EFFECTIVE DATE: January 11, 1993.

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of April 15, 1992 (57 FR 13234), FDA published proposed procedures under which the agency would accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provision for required continued study of the drugs' clinical benefits after approval or for restrictions on distribution or use, where those are necessary for safe use of the drugs. FDA provided 60 days for public comment, and, upon request, in the **Federal Register** of June 18, 1992 (57 FR 27202), extended the comment period for an additional 30 days until July 15, 1992. The final rule incorporates all of the provisions of the proposed rule and provides additional clarification regarding both timing and content of the submissions of promotional materials and regarding the nature of required postmarketing studies. The agency has added a new provision clarifying when certain postmarketing requirements of the rule will be terminated.

Highlights of the final rule are summarized below, followed by a summary and discussion of the comments.

II. Highlights of the Final Rule

This final rule establishes procedures under parts 314 and 601 (21 CFR parts 314 and 601) under which FDA will accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provision for required continued study of the drugs' clinical benefits after approval or for restrictions on distribution or use, where those are necessary for safe use of the drugs. These procedures are intended to provide expedited marketing of drugs for patients suffering from such illnesses when the drugs provide meaningful therapeutic advantage over existing treatment. The preamble of the proposed rule (57 FR 13234) provides a description of other mechanisms available to facilitate access, speed development, and expedite review of therapeutic products (e.g., treatment investigational new drug applications (IND's), subpart E, parallel track). Where appropriate, these mechanisms can be utilized in concert with accelerated approval. The major provisions of the final rule are as follows:

A. Scope

The new procedures apply to certain new drug, antibiotic, and biological products used in the treatment of serious or life-threatening diseases, where the products provide meaningful therapeutic advantage over existing treatment (21 CFR 314.500 and 601.40).

B. Criteria for Approval

Accelerated approval will be considered in two situations: (1) When approval can be reliably based on evidence of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity, pending completion of studies to establish and define the degree of clinical benefits to patients; and (2) when FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted. Drugs or biological products approved under this final rule will have met the requisite standards for safety and effectiveness under the act or the PHS Act and, thus, will have full approval for marketing (21 CFR 314.510, 314.520, 601.41, and 601.42). Ordinarily, products used to treat serious or life-threatening illnesses, for which approval is based on a surrogate endpoint that is recognized as validated by definitive studies, will be considered for approval under the traditional process rather than under accelerated approval.

C. Postmarketing Studies

Where a drug's approval under these provisions is based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity, the applicant will be required to conduct clinical studies necessary to verify and describe the drug's clinical benefit and to resolve remaining uncertainty as to the relation of the surrogate endpoint upon which approval was based to clinical benefit, or the observed clinical benefit to ultimate outcome. The requirement for any additional study to demonstrate actual clinical benefit will not be more stringent than those that would normally be required for marketing approval; it is expected that the studies will usually be underway at the time of approval. The proposed regulations have been revised to clarify that required postmarketing studies must also be adequate and well-controlled (21 CFR 314.510 and 601.41).

D. Restrictions on Use After Marketing

FDA may grant marketing approval of a drug or biological product shown to be effective where safe use can only be assured if distribution or use is restricted. Under this final rule, FDA may: (1) Restrict distribution to certain facilities or to physicians with special training or experience, or (2) condition distribution on the performance of

specified medical procedures. The restrictions on use will be tailored to the specific safety issue raised by the particular drug or biological product and agreed to by the applicant at the time of approval (21 CFR 314.520 and 601.42). FDA expects that the imposition of these restrictions on distribution will be rare.

E. Promotional Materials

The final rule requires submission of planned promotional materials, including promotional labeling and advertisements, both prior to approval (reflecting the initial campaign), and following approval, unless informed by the agency that such submission is no longer necessary, at least 30 days before the intended time of initial dissemination of the promotional labeling or initial publication of the advertisement (21 CFR 314.550 and 601.45).

F. Withdrawal of Approval

The final rule establishes an expedited procedure for the withdrawal of approval if: (1) Postmarketing clinical studies fail to verify clinical benefit; (2) the applicant fails to perform the required postmarketing study with due diligence; (3) use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the drug or biological product; (4) the applicant fails to adhere to the postmarketing restrictions agreed upon; (5) the promotional materials are false or misleading; or (6) other evidence demonstrates that the drug or biological product is not shown to be safe or effective under its conditions of use (21 CFR 314.530 and 601.43).

G. Termination of Requirements

In response to comments, the final rule provides that the requirements set forth in §§ 314.520, 314.530, and 314.550 for new drugs and antibiotics and §§ 601.42, 601.43, and 601.45 for biological products ordinarily will terminate when FDA determines that the results of required postmarketing studies have demonstrated that the drug or biological product has clinical benefit, or, where restrictions on distribution or use have been imposed, when FDA determines that safe use of the drug or biological product can be ensured without such restrictions, e.g., through appropriate labeling. FDA will notify the applicant when these requirements no longer apply (21 CFR 314.560 and 601.46).

III. Effective Date

This regulation will become effective on January 11, 1993.

IV. Comments on the Proposed Rule

FDA received 54 comments on the proposed rule. The comments came from individuals, specific disease organizations, universities, pharmaceutical manufacturers, trade associations, health professionals, and professional societies. The comments reflect broad support and acceptance of the goal of expediting the approval of drugs intended for the treatment of serious and life-threatening illnesses. A number of comments asked that the proposal be finalized expeditiously without change. Many comments posed specific questions and raised important concerns.

A. General Comments

1. One comment suggested that the term "conditional approval" was less confusing and ambiguous than the term "accelerated approval." The comment also referred to the statement in the proposal that "Drugs * * * approved under this proposal will have met the requisite standards * * * under the (act)" and argued that because postmarketing conditions may be imposed, this statement can only be read to say that the requisite standards under the act can only be met by a lower standard of evidence in hand, combined with assurance that further evidence will be obtained.

Another comment expressed concern that the proposal appears to establish a standard for the evaluation of drug product effectiveness that is inconsistent with the substantial evidence requirement of section 505(d) of the act (21 U.S.C. 355(d)), which means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling * * *." The comment argued that, with few exceptions, the agency has consistently interpreted the "substantial evidence" requirement as an instruction that determinations of effectiveness be based on data unambiguously reflecting the clinical status of subjects evaluated under controlled conditions in bona fide clinical experiments. In the absence of compelling empirical evidence documenting that a drug-induced change in a surrogate measure reliably and consistently predicts improved clinical outcome, a surrogate indicator is no more than a hypothetical construct. The comment asserted that the proposed rule's endorsement of the use of unvalidated surrogate endpoints, therefore, appears to represent a significant departure from traditional agency interpretations of "substantial evidence" within the meaning of the act because it allows belief rather than evidence to serve as the basis for a conclusion about the effectiveness of a new drug.

Three comments asserted that the new regulations are not needed to approve drugs intended to treat serious or life-threatening illnesses. Two comments cited FDA's approval, without new regulations, of didanosine (formerly called ddi) and zalcitabine (formerly called ddc) in combination with zidovudine (formerly called AZT) based on a surrogate marker, i.e., an increase in CD4 cell counts and the "subpart E" procedures at 21 CFR part 312, which address the need for expediting the development, evaluation, and marketing of new therapies intended to treat life-threatening or severely debilitating illnesses as examples of existing mechanisms for the expedited approval of important new drugs. One comment argued that the act requires that drugs be shown to be "safe" and "effective," and proof of effectiveness is not limited by the act to demonstration of an effect on "survival or irreversible morbidity," as the proposed rule seems to assume. The comment further argued that FDA has considerable statutory discretion to define what type of data constitutes proof of effectiveness, and demonstration of an effect on a surrogate marker is one type of such proof.

The agency believes that what the procedures are called is much less important than what the procedures are. The shorthand term selected by the agency reflects the intent of the rule, especially that part related to use of surrogate markers, which is to make drugs that provide meaningful improvement over existing therapies for serious illnesses widely available (through marketing) at the earliest time consistent with the law. The essence of the proposal is thus acceleration, not the imposition of conditions. Approval under these procedures is dependent on compliance with certain additional requirements, such as timely completion of studies to document the expected clinical benefit. The evidence available at the time of approval under this rule will meet the statutory standard, in that there must be evidence from adequate and well-controlled studies showing that the drug will have

the effect it is represented to have in its labeling. That effect will, in this case, be an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit and labeling will refer to the effect on the surrogate, not to effect on clinical outcome.

While the act does not refer to particular endpoints or state a preference for clinical, as opposed to surrogate, endpoints, it is well established that the effect shown in well-controlled studies, must, in the judgment of the agency, be clinically meaningful. Moreover, the safety standard in the act, that a drug must be shown to be safe for its intended use, implies a risk/benefit judgment. The effect shown must be such as to outweigh the risks of the treatment under the conditions of use. Approval under this rule requires, therefore, that the effect shown be, in the judgment of the agency, clinically meaningful, and of such importance as to outweigh the risks of treatment. This judgment does not represent either a "lower standard" or one inconsistent with section 505(d) of the act, but rather an assessment about whether different types of data show that the same statutory standard has been met.

Approval based on surrogate endpoints is not new, although the issue has not previously been considered in regulations. The agency has, in a number of instances, approved drugs based on surrogate endpoints. For example, drugs for hypertension have been approved based on their effects on blood pressure rather than on survival or stroke rate. Similarly, drugs for hypercholesterolemia have been approved based on effects on serum cholesterol rather than on coronary artery disease (angina, heart attacks). But, in those cases there was very good evidence from clinical trials (in the case of hypertension) and from epidemiologic and animal studies (in the case of hypercholesterolemia) that improving the surrogate would lead to or is associated with the desired effects on morbidity and mortality. Even so, there is still today considerable debate about who will benefit from cholesterol lowering. Controlled trials assessing effects on clinical endpoints of morbidity and mortality from use of cholesterol-lowering drugs have been, and are being, conducted.

Reliance on a surrogate endpoint almost always introduces some uncertainty into the risk/benefit assessment, because clinical benefit is not measured directly and the quantitative relation of the effect on the surrogate to the clinical effect is rarely known. The expected risk/benefit relationship may fail to emerge because: (1) The identified surrogate may not in fact be causally related to clinical outcome (even though it was thought to be) or (2) the drug may have a smaller than expected benefit and a larger than expected adverse effect that could not be recognized without large-scale clinical trials of long duration. Reliance on surrogate markers therefore requires an additional measure of judgment, not only weighing benefit versus risk, as always, but also deciding what the therapeutic benefit is based upon the drug effect on the surrogate.

The sections of the final rule that address approval based upon a drug effect on a surrogate endpoint specifically clarify the regulatory approval criteria when the agency relies on a surrogate endpoint that, while "reasonably likely" to predict clinical benefit, is not so well established as the surrogates ordinarily used as bases of approval in the past. Postmarketing studies required to verify and describe actual clinical benefits would also be required to be adequate and well-controlled studies. Sections 314.510 and 601.41 have been revised to clarify this point. If, on completion of required postmarketing studies, the effect on the surrogate is not shown to correspond to a favorable effect on clinical benefit, the rule provides an expedited means of removing the drug from the market.

Approval of didanosine and zalcitabine under current procedures does not show that the rule is of no value. Although approval did rely on a surrogate endpoint that is of the kind specifically addressed by the rule, the fact that studies to define clinical benefit were nearly complete and were being conducted under the auspices of the National Institute of Allergy and Infectious Diseases made it less crucial to have additional guarantees that such studies would be conducted promptly. Moreover, the sponsors of didanosine and zalcitabine agreed prior to approval to expedited withdrawal of the drug from the market if benefit were not shown. The provisions of the final rule will ensure that appropriate safeguards exist for timely generation of data on actual clinical benefit, for appropriate promotional information about labeled indications, and for prompt withdrawal of the drug from the market if clinical benefit is not confirmed.

2. Pointing to a statement in the preamble to the proposed rule that it is in the public interest to make promising new treatments available at the earliest possible point in time for use in life-threatening and serious illnesses, one comment expressed concern that the proposed rule may lead to the marketing of large numbers of clinically ineffective, but pharmacologically active, drugs and this may not be in the interest of the public health. The comment argued that early access to so-called "promising" drugs is not the same as early access to safe and effective drugs, and the number of potential markers that may be advanced as surrogates of clinical outcome is exceedingly large. The comment suggested that it may be more appropriate to seek adoption of the proposed requirements through an amendment to the act.

FDA agrees with the contention that providing people who have serious or life-threatening illnesses with numerous clinically ineffective drugs would not be helpful. However, the agency does not agree that the rule can be expected to have this result. Although studies using surrogate endpoints may provide less assurance of clinical benefit than studies using clinical endpoints, FDA believes compliance with all of the elements of the accelerated approval program will not result in the marketing of large numbers of clinically ineffective drugs. The new procedures apply to a limited group of circumstances, namely, to drugs intended for serious or life-threatening illnesses when the drugs provide a meaningful therapeutic benefit over existing therapy. Reliance on a surrogate endpoint is not equivalent to reliance on any evidence of pharmacologic activity. The endpoint must be reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit.

Whether a given endpoint is, in fact, reasonably likely to predict clinical benefit is inevitably a matter of judgment. FDA, using available internal and external expertise, will have to make informed judgments in each case presented, just as it does now. The agency acknowledges that there are well-recognized reasons for caution when surrogate endpoints are relied on. Certain putative surrogates have ultimately been shown not to correspond to clinical benefit. Perhaps the most noteworthy example is the failure of antiarrhythmic agents in the Cardiac Arrhythmia Suppression Trial (CAST) to improve survival by depressing ventricular ectopic beats; effective suppression of ectopic beats was associated with increased mortality.

A sponsor must persuasively support the reasonableness of the proposed surrogate as a predictor and show how the benefits of treatment will outweigh the risks. Such presentations are likely to be persuasive only when the disease to be treated is particularly severe (so

that considerable risk is acceptable) and/or when the surrogate endpoint is well supported. In addition, it will be the sponsor's clear obligation to resolve any doubts as to clinical value by carrying out definitive studies.

FDA does not agree that it would be more appropriate to seek an amendment to the act than to adopt the proposed requirements. As discussed in the preamble to the proposed rule as well as elsewhere in this preamble to the final rule, existing provisions of the act and the PHS Act authorize promulgation of the requirements in the final regulations.

3. One comment expressed concern that because the proposed rule would establish conditions on a drug's approval, third-party payors may decline reimbursement because the so-called approval would have attributes of investigational status.

The agency expects that, because drugs approved under the accelerated approval process meet the statutory standards for safety and effectiveness, they would be eligible for reimbursement under State Medicaid programs or other third-party plans. Drug products granted accelerated approval will not be, under the law, investigational, as suggested by the comment.

4. One comment asked if all drugs considered for accelerated approval must be reviewed by an advisory committee. The comment stated that because advisory committees meet infrequently, waiting for the next meeting may slow down the approval process.

FDA is not required to consult with an advisory committee before approving an application under these accelerated approval regulations, or any other regulation. However, FDA intends to consult the appropriate committee in most instances. Advisory committee meetings can usually be scheduled to avoid significant delays in the review process. The agency will consider any request by an applicant for referral of the application to an advisory committee.

B. Scope

5. Four comments asked for further clarification of what diseases are covered by the rule. One comment stated that the terms "serious," and "life-threatening," are defined in the proposal by reference to 21 CFR 312.34, followed by a brief statement explaining the role of judgment and examples of diseases that are currently judged to be serious. The comment asked that FDA also describe: (1) Diseases that are not currently included in the category of "serious," (2) examples of diseases that are currently judged "life-threatening," and (3) examples of diseases that are not currently included in the category "life-threatening."

One comment contended that the statement in the preamble that "seriousness of a disease is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one" too narrowly limits diseases covered by the proposed rule (57 FR 13234 at 13235). The comment argued that some "less severe" diseases, even if treated, may progress to a more serious state, and that these diseases should also be covered by the rule. On the other hand, two comments argued that the language in the preamble that classifies diseases as "serious" was overly broad and subjective and far too large a number of illnesses could be eligible as being "serious."

FDA discussed the meaning of the terms "serious" and "life-threatening" in its final rules on "treatment IND's" (52 FR 19466 at 19467, May 22, 1987) and "subpart E" procedures (54 FR 41516 at 41518–41519, October 21, 1988). The use of these terms in this rule is the same as FDA defined and used the terms in those rulemakings. It would be virtually impossible to name every "serious" and "life-threatening" disease that would be within the scope of this rule. In FDA's experience with "treatment IND's" and drugs covered by the "subpart E" procedures there have not been problems in determining which diseases fall within the meaning of the terms "serious" and "life-threatening," and FDA would expect no problems under this accelerated approval program. The likelihood of progression to a serious condition with available treatments would also be considered in assessing whether the disease is within the scope of the final rule. The preamble to the proposed rule (57 FR 13234 at 13235) referred to chronic illnesses that are generally well managed by available therapy, but can have serious outcomes for certain populations or in some or all of their phases. Applicants are encouraged to consult with FDA's reviewing divisions early in the drug development process if they have questions about whether their specific product is within the scope of this rule.

The concerns expressed in these and other comments about considering too many illnesses eligible for consideration under the accelerated approval procedures may arise from the underlying fear that reliance on surrogate endpoints will become routine, the "normal" way drugs are brought to the market. This fear is groundless. The vast majority of drugs are directed at symptomatic or short-term conditions (pain, heart failure, acute infections, gastrointestinal complaints) whose response to drugs, if it occurs, is readily measured and where there is no need to consider or accept surrogate endpoints. Surrogates, with few exceptions, are of interest in the following situations: (1) Where the clinical benefit, if there is one, is likely to be well in the future; and (2) where the implications of the effect on the surrogate are great because the disease has no treatment at all or the drug seems to treat people with no alternative (e.g., because they cannot tolerate the usual effective treatment). In the first case, great care is needed, and would be given, as there would generally be no experience linking an effect on the surrogate to clinical success, and there have been conspicuous examples of lack of linkage (CAST, referred to above; drugs that increase cardiac output in patients with heart failure but that decrease survival; imperfect agreement of effects on coronary artery patency and effects on survival in patients with myocardial infarction; lack of beneficial effect on bone fracture rate despite favorable effects on bone density in patients with osteoporosis). FDA and outside experts will be aware of these examples as proposed surrogates are considered. The implications are especially great when considering prophylactic therapy, i.e., treatments to prevent chronic illness (coronary artery disease, cancer), in an essentially well population. In the second case, there will generally have been experience (with the standard therapy) to evaluate in considering linkage of the surrogate to benefit; this was, for example, the case with didanosine, where evidence from zidovudine studies of the relationship of an effect on CD4 lymphocytes and clinical outcome could be assessed. Similarly, there is considerable experience to show that durable complete responses in many cancers correspond to improved survival, so that an agent inducing them in refractory illness or in primary

disease that had previously been poorly responsive would generally be seen as reasonably likely to provide a clinical benefit.

6. One comment stated that epilepsy is a serious and life-threatening condition and asked that it be included within the scope of the proposal. The preamble cited, among other illnesses, depression and psychoses as examples of chronic illnesses that can have serious outcomes even if they are generally well managed. One comment asserted that neither depression nor psychosis is a disease, nor is either one serious or life-threatening. The comment stated that depression and psychosis are diagnoses. The comment urged the agency to remove them from the definition of life-threatening "illnesses" or "diseases."

With respect to epilepsy, FDA notes that in the "treatment IND" final rule (52 FR 19466 at 19467, May 22, 1987), the agency listed "certain forms of epilepsy" as an example of a disease or stage of disease that would normally be considered "serious." Certain forms of epilepsy may also be considered "serious" under the accelerated approval program. It is unlikely, however, that a surrogate endpoint would be utilized in such a case, as seizure frequency, a clinical endpoint, is readily measured.

FDA's reference to depression and psychoses was intended to give examples of conditions or diseases that can be serious for certain populations or in some or all of their phases. While drugs for the treatment of depression and psychosis would be examples of those that could be covered by the accelerated approval program, it is not the use of surrogate endpoints that would be expected; the symptoms and signs of these diseases are readily studied. On the other hand, some of these drugs have been quite toxic (e.g., clozapine for refractory psychoses) and might be considered for approval with restrictions to ensure safe use.

7. Two comments asked how FDA will decide that a drug is eligible for accelerated approval. One comment asserted that the decision should be an option for the applicant to consider, not a decision for FDA to make unilaterally. Pointing to a statement in the preamble (57 FR 13234 at 13235) that FDA reserves the right not to apply accelerated approval procedures when it believes in good faith that the drug's foreseeable use is reasonably likely to be outside the scope of "life-threatening diseases without meaningful therapeutic benefit over existing therapy," the comments argued that, if there are patients with life-threatening conditions that can benefit from expedited approval, the needs of the patients should determine the procedures used to approve the drug. One comment contended that applicants of products considered candidates for accelerated approval may have their drug or biological product "forced" into the accelerated approval process and be forced to conduct a program of studies to substantiate that surrogate endpoints actually predict significant clinical benefits.

The medical reviewing divisions within FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) will determine the type of regulatory review that FDA may apply to an application. FDA encourages sponsors to meet with FDA early in the drug development process to discuss the applicability of the accelerated approval program to their product; however, FDA reserves the discretion to determine whether these procedures are applicable to a specific product.

With respect to the preamble statement cited by one comment, the comment misreads the preamble statement, which does not say that FDA will, in all cases, apply FDA's traditional approval mechanisms rather than this accelerated process for drugs where a majority of the drug's foreseeable uses are outside the scope of "life-threatening" diseases without meaningful therapeutic benefit over existing therapy. The statement merely informs applicants that FDA will consider the possible impact of widespread use of a drug for uses other than the one supporting accelerated approval; drugs approved under this program would often have only small safety data bases so that widespread off-label use might have serious implications. The agency does not believe that such a situation would regularly lead to exclusion from these provisions.

FDA does not agree that applicants seeking approval to market drug and biological products that would be candidates for accelerated approval will be forced to use the accelerated approval mechanism. It is true, however, that some proposed surrogate endpoints would not be considered acceptable bases for approval without assurance that the clinical studies to show clinical benefit will be conducted. A sponsor that wishes the application to be considered under the traditional approval process may request and receive such consideration.

The agency wishes to clarify the circumstances in which the accelerated approval regulations will apply. Sections 314.500 and 601.40 describe aspects of the scope of these regulations. Moreover, these regulations are intended to apply to applications based on surrogate endpoints whose validity is not fully established, to applications based on clinical endpoints that leave unanswered major questions about the product's effect on ultimate outcome, and to applications for products whose safe and effective use requires limitations on distribution or use. In all other situations, accelerated approval requirements will not apply.

Where approval is based on a surrogate endpoint that is accepted as validated to predict or correlate with clinical benefit, the product will be considered under the traditional process, and the postmarketing requirements under accelerated approval will not apply. Approvals of products for serious or life-threatening illnesses based on clinical endpoints other than survival or irreversible morbidity will usually also be considered under traditional procedures. Approvals based on such clinical endpoints will be considered under the accelerated approval regulations only when it is essential to determine effects on survival or irreversible morbidity in order to confirm the favorable risk/benefit judgment that led to approval. Applications for products for serious or life-threatening illnesses that provide a meaningful therapeutic benefit over existing therapy will receive a priority rating and expedited review, even when not considered under the accelerated approval procedures.

The agency also wishes to clarify that whenever an application is approved under § 314.510 or § 601.41, postmarketing studies confirming the product's clinical benefit will thus be required. Therefore, in order to eliminate potential confusion, the agency has amended §§ 314.510 and 601.41 to clarify these points.

FDA also recognizes that over time a particular surrogate, once acceptable as a basis for approval only under the accelerated approval regulations, could become recognized as validated by definitive studies (just as high blood pressure, for example, over time became validated as a surrogate with clinical significance). In such cases, a future application relying on such a surrogate would not require postmarketing studies confirming the surrogate's clinical benefit and the application would be considered under traditional procedures.

8. Two comments asked for clarification of the phrase "meaningful

therapeutic benefit over existing therapy" as used in the description of what drugs the accelerated approval program should apply to. Specifically, pointing to an example described in the preamble that a new therapy would be eligible for accelerated approval if there was "a clear improvement" over existing therapy in being more effective or better tolerated, one comment urged FDA to clarify the meaning of "clear improvement" to discourage applicants of "me-too" products from wasting the agency's time and resources by applying for accelerated approval of such products. The comment also asked that FDA specify that if a new drug is approved under the accelerated approval provisions because the drug exhibits a "clear improvement" over an existing drug that was also granted accelerated approval, then specific restrictions will be placed on the prior approved drug to limit its use only to patients who cannot tolerate the new drug, or whose physicians assess that a change to the new drug might involve significant risks to the patient that outweigh the benefits. One comment asked that the term "meaningful therapeutic benefit over existing therapy" be interpreted and consistently applied to both drugs and biological products.

FDA believes that the examples given to help clarify the phrase "meaningful therapeutic benefit over existing therapy" (ability to treat unresponsive or intolerant patients or improved response compared to available therapy) are readily understood illustrations of the intent of the requirement. A drug that is essentially the same as available treatment (what the comment refers to as a "me too" drug) will not have a credible claim to a meaningful therapeutic benefit over that existing treatment and this should be easily detected.

With respect to restricting use of a drug previously approved under accelerated approval procedures when a new drug granted accelerated approval is a clear improvement over the prior approved drug, this would rarely be appropriate. Although, in some instances, certain therapies are identified as "second-line," this requires essentially unequivocal evidence of an advantage of alternative therapy, not likely on the basis of a surrogate endpoint. Labeling for both drugs will be accurate, however, allowing physicians to prescribe both the newly approved drug and the prior drug properly.

9. One comment asked if a change in the route of administration would be considered as a meaningful benefit and within the scope of the proposal.

A change in the route of administration may be a candidate for accelerated approval depending upon the particular evidence presented.

10. One comment asked if subpart E drugs currently under investigation will be considered for accelerated approval. The comment assumed that new drug applications (NDA's) and supplemental NDA's considered for accelerated approval will have the highest priority for review.

Subpart E drugs will be considered for accelerated approval if they satisfy both eligibility criteria for accelerated approval, i.e., if they are being developed for the treatment of serious or life-threatening illnesses and the products will provide meaningful therapeutic benefits to patients over existing treatment. As discussed above, applicants should consult with FDA early in the development process to determine the nature of the regulatory review. Early consultations are a critical part of subpart E procedures. Drugs being reviewed under accelerated approval procedures will receive high priority review. However, applications for drugs for acquired immunodeficiency syndrome (AIDS) and human immunodeficiency virus (HIV)-related conditions will receive the highest priority review.

C. Criteria for Approval

11. Two comments expressed concern that the proposal did not provide enough detail on what constitutes an appropriate surrogate endpoint. One comment recommended that FDA adopt specific criteria for what constitutes an appropriate surrogate endpoint. The comment suggested that such criteria should include: (1) The surrogate endpoint must be biologically plausible in that it must be consistent with what is known about the pathophysiology and pathogenesis of the disease; (2) the surrogate endpoint must be present or abnormal in a large percentage of people who have the disease; (3) the surrogate endpoint must be a good predictor of the disease progression and should correlate closely with the significant clinical endpoint; (4) there should be a correlation between the quantitative aspect of the surrogate endpoint and the progression of the disease (e.g., the more severe the disease, the more deviant the surrogate endpoint from normal); (5) the regression of the surrogate endpoint should be significantly associated with clinical improvement (e.g., those with the greatest improvement in the surrogate endpoint should also show the greatest clinical effects); conversely, the lack of regression of the surrogate endpoint should be commonly associated with a lack of clinical improvement; and (6) the incidence of regression or improvement in the surrogate endpoint should be significantly greater in treated than untreated patients.

One comment asked if the use of microalbuminuria data is a surrogate for diabetic nephropathy and if all drugs relying on surrogate endpoints would be eligible for accelerated approval, e.g., an angiotensin receptor antagonist with potential utility for treatment of congestive heart failure. The comment also asked what would happen if postmarketing studies demonstrate beneficial changes of surrogate endpoints but not beneficial clinical endpoints. The comment also asked if FDA will consider publishing guidelines on which surrogate endpoints would be appropriate for the diseases that may be affected by the proposed rule. Another comment expressed the belief that there is no evidence that surrogate endpoints are necessarily good indicators of therapeutic benefit. The comment stated that a drug may have an effect on a surrogate endpoint, but will not make any clinical difference because the advanced stage of the patient's disease precludes any effective therapy or the surrogate marker is not synchronous with the patient's clinical condition.

Another comment asserted that the requirement to base an approval on a surrogate endpoint that is "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit other than survival or irreversible morbidity" is not restrictive enough to assure adequate consumer protection. Terms like "reasonably likely" and "or other evidence" allow drug manufacturers too much latitude for claiming that there is a correlation between surrogate endpoints affected by their drugs and clinical endpoints. The comment argued that until a correlation between a surrogate endpoint and a clinical endpoint has been established, a particular surrogate endpoint should only be used to approve subsequent drugs, without adequate clinical evidence, if there is a very strong effect of the drug on the surrogate marker or, if the effect is not sufficiently strong, there is an additional surrogate marker which corroborates the results of the first.

FDA intends to publish informal guidance concerning surrogate endpoints, but does not believe specific requirements for an appropriate surrogate should be specified by

regulation. Any given specifications may not be applicable to a particular case. For example, the thoughtful suggested criteria supplied by the comment would rarely, if ever, be applicable to the first effective drug for a disease, because criterion 5 requires that regression of the surrogate endpoint be associated quantitatively with clinical improvement. If there had never been effective treatment, this would never be known. Yet the surrogate could be persuasive on other grounds, such as a well-documented etiologic relation. In general, it is likely that one or another strongly supportive piece of evidence might outweigh gaps in other areas.

In developing informal guidance on surrogate endpoints, FDA will consider the suggestions in this comment. Interested persons will have an opportunity to comment on any guidance documents in this area developed by the agency. In some cases, new or revised drug class, or disease-specific, clinical guidelines may refer to surrogate endpoints. FDA is not prepared, at this time, to comment on the acceptability of an endpoint that it has not specifically considered, e.g., microalbuminuria.

The final regulations make it clear that not all drugs submitted for approval based on surrogate endpoint data are eligible for accelerated approval (§§ 314.500 and 601.40). The drug in question must be for a serious or life-threatening condition and must provide meaningful therapeutic benefit over existing therapy. In the case of an angiotensin receptor antagonist posed by the comment, there is existing documented life-prolonging treatment for congestive heart failure. An application for a new agent, to be eligible for accelerated approval, would have to show potential benefit over available therapy as well as identify a reasonable surrogate endpoint. This is problematic since no accepted surrogate endpoint for studies to treat congestive heart failure has been identified to date. For example, some drugs with favorable effects on hemodynamic measures in heart failure patients have been clinically ineffective.

The regulations are clear in requiring that, for drugs approved under these provisions based on surrogate endpoints, the postmarketing studies must show clinical benefit, not just the previously shown effect on the surrogate (§§ 314.510, 314.530, 601.41, and 601.43).

Surrogates, or proposed surrogates, are not always good, nor necessarily bad, indicators of therapeutic benefit and must be judged on a case-by-case basis. Even very good surrogates may not be perfect: Blood pressure lowering has been a better predictor of effect on stroke than on coronary artery disease, cholesterol lowering has had a clearer effect on coronary artery disease than on survival. Moreover, a surrogate may be persuasive for a phase of disease with short expected survival but much less so in an earlier phase of the disease. Caution is always appropriate in evaluating surrogate endpoints and the particular therapeutic setting should always be considered. The agency believes that the evaluation of surrogate endpoint data and the safeguards built into these accelerated approval procedures will provide adequate consumer protection.

12. One comment expressed concern that if there is no accepted surrogate endpoint, an applicant's only option is to conduct a study using some clinical event as an endpoint, which may result in long, large studies that delay approval to the detriment of patients and sponsors. One comment suggested as an alternative that FDA permit approval of a drug based on a study using a clinical endpoint, but accept a less rigorous standard of statistical significance, e.g., 0.20 or 0.15 instead of 0.05. The comment further suggested that the sponsor could then complete postmarketing studies to establish statistical significance at conventional levels. The comment argued that this alternative is totally consistent with FDA's willingness to accept greater uncertainty in approving drugs for serious and life-threatening illnesses.

The intent of the rule is to allow FDA to utilize a particular kind of evidence, an effect on a surrogate endpoint, as a basis for approval, and, where appropriate, to ensure that remaining doubts about the relationship of the effect on the surrogate to clinical benefit are resolved by additional adequate and well-controlled studies with clinical endpoints. The rule is not intended to place into the market drugs with little evidence of usefulness. Although there is no statutory requirement for significance testing of any particular value, there are well-established conventions for assessing statistical significance to support the statutorily required conclusion that the well-controlled studies have demonstrated that a drug will have the effect it is represented to have. There is nothing about serious or life-threatening diseases that make them uniquely difficult to study. A meaningful effect on survival or morbidity where there is no effective therapy should be readily discerned. Such studies need be long and large only when the effect is small or difficult to detect. In that event, proper assessment of benefit, and valid weighing of its relation to risk, is especially critical.

13. One comment asked that FDA clarify that one study could be the basis of approval and that one postmarketing study should be all that is needed to establish the link between the endpoint used for approval and some relevant clinical benefit.

FDA interprets the statute, and good science, as requiring at least two adequate and well-controlled studies to establish effectiveness. In some instances, drugs have been approved on the basis of a single well-controlled study; this has been done where the study was of excellent design, showed a high degree of statistical significance, involved multiple study centers, and showed some evidence of internal replicability, e.g., similar effects in major study subsets. FDA encourages applicants to discuss with FDA early in a drug's development the basis for the applicant's choice of a specific endpoint and, where applicable, the basis for its belief that a single study would be a sufficient basis for approval. With respect to postmarketing studies, FDA anticipates that the requirement will usually be met by studies already underway at the time of approval. As stated in the proposed rule, the requirement for any additional study to demonstrate actual clinical benefit will not be more stringent than those that would normally be required for marketing approval of the same drug for the same claim.

14. One comment expressed concern that the preamble to the proposed rule implied that a sponsor of an AIDS drug might have to do a postmarketing study to establish an effect on survival after showing an effect on such endpoints as weight or incidence of opportunistic infection (57 FR 13234 at 13235–13236). The comment stated that FDA's own advisory committee indicated that it was pleased to see an effect from a nucleoside analogue on the incidence of opportunistic infections with AIDS patients but did not suggest that further work should be done to show an effect on mortality. The comment argued that in some cases direct correlation with clinical endpoints such as mortality is difficult to prove and urged FDA to be flexible on this issue to encourage sponsors to go through the accelerated approval process.

Ordinarily, an effect on a meaningful clinical endpoint, e.g., on rate of opportunistic infections in AIDS, is a sufficient basis for approval without need for followup studies. Other endpoints, however, might leave major questions unanswered. For example, a

modest effect on weight gain in AIDS without other demonstrated benefit, if considered an adequate basis for approval, while a clinical endpoint, might leave sufficient doubt as to the ultimate value of the effect so that further studies would be necessary. FDA intends to interpret this provision of the regulations with flexibility. This provision should also serve as a reminder, however, that for life-threatening diseases, the ultimate aim of therapy is improved survival as well as improved symptoms.

15. One comment asked FDA to clarify what a sponsor's obligation is to continue supplying medication on a compassionate basis if clinical efficacy is not demonstrated to FDA's satisfaction in postmarketing studies but individual patients appear to be benefiting from use of the drug.

Sponsors are not obligated to supply drugs on a "compassionate basis." Whether, if clinical studies did not show effectiveness, further availability of the drug would be appropriate under any mechanism would be determined case-by-case.

D. Promotional Materials

16. Three comments asserted that requiring advance submissions of promotional materials is both beyond FDA's statutory authority and is unnecessary. Although FDA stated in the proposal that it does not intend specifically to approve promotional materials, two comments contended that is the likely effect of advance submission. The comment cited section 502(n) of the act (21 U.S.C. 352(n)), which provides that no regulation promulgated under that provision shall require prior FDA approval of the content of any advertisement "except in extraordinary circumstances," and asserted that the "extraordinary circumstances" language would not apply to drugs approved under the accelerated approval program. One comment argued that submission of promotional material prior and subsequent to approval is unwarranted when dealing with treatments for serious or life-threatening illnesses where dissemination of the most current and timely information is important to the treating physician. One comment questioned why there would be any greater likelihood of misleading promotional claims for products approved under the proposed accelerated approval process than for drugs intended to treat serious or life-threatening diseases that are approved under the normal NDA procedures. The comment also expressed the hope that the proposed requirement for advance submission of promotional materials was not based upon an assumption that promotional materials for drugs intended to treat serious diseases are more likely to be misleading than promotional materials for other types of drugs because any such assumption would be unfounded. One comment argued that if an advertisement or labeling is inaccurate, the product is misbranded and FDA could then obtain injunctive relief, seize the product, and/or initiate criminal proceedings. Another comment considered requiring advance submission of promotional materials unreasonable because companies are not required to do so now. One comment questioned the legal authority for requiring presubmission of promotional material following approval of a drug product, and the reason for the requirement.

The agency believes that the requirements for submission of promotional materials in the context of accelerated approval are authorized by statute. Subsections 505(d)(4) and (d)(5) of the act provide that, in determining whether to approve a drug as safe and effective, the agency may consider not only information such as data from clinical studies but also "any other information" relevant to safety and effectiveness under the proposed conditions of use. Such information would include information about how the drug would be promoted. In determining whether the drug's proposed labeling would be "false or misleading" under section 505(d)(7) of the act, the agency is similarly authorized to evaluate "all material facts" during the approval process, including the facts about promotion.

FDA is also authorized by section 505(k) of the act to require reporting of information subsequent to approval necessary to enable the agency to determine whether there may be grounds for withdrawing the approval. Among the grounds for withdrawal specified in section 505(e) of the act are that the evidence reveals the drug is not shown to be safe and effective under its conditions of use. In addition, drug approval may be withdrawn if information shows the labeling to be false or misleading. Information on how the drug will be promoted is again relevant to whether the drug's marketing approval should be withdrawn. Section 701(a) of the act (21 U.S.C. 371(a)) generally authorizes FDA to promulgate regulations for the efficient enforcement of the act.

For biological products, additional authority in section 351 of the PHS Act (42 U.S.C. 262) authorizes the promulgation of regulations designed to ensure the continued safety, purity, and potency of the products. The content of promotional materials is important to the continued safe and effective use of biologicals.

Therefore, the provisions of the final rule requiring submission of promotional materials prior to approval under the accelerated approval procedures and subsequent to such approval are authorized by statutory provisions. FDA might also invoke the authority of section 502(n) of the act (21 U.S.C. 352(n)) to require prior approval of the content of any prescription drug advertisement in "extraordinary circumstances." Whether FDA could appropriately rely on section 502(n) of the act in promulgating §§ 314.550 and 601.45 need not be determined, however, because FDA is not relying upon section 502(n) of the act as legal authority for these (or any other) sections of the accelerated approval regulations.

The agency believes that advance submissions of promotional materials for accelerated approval products are warranted under the accelerated approval circumstances. The special circumstances under which drugs will be approved under these provisions and the possibility that promotional materials could adversely affect the sensitive risk/benefit balance justify review of promotional materials before and after approval. For example, if the promotional materials exaggerate the known benefits of the drug, wider and inappropriate use of the drug could be encouraged, with harmful results.

Similarly, high risk drugs that are approved based on postmarketing restrictions would not have been approved for use without those restrictions because the risk/benefit balance would not justify such approval. If promotional materials were to undermine the postmarketing restrictions, the health and safety of patients could be greatly jeopardized.

Although there is potential harm from any misleading promotion, and there is no reason to believe improper promotion is more likely in this setting than in others, the risk/benefit balance is especially sensitive in this setting. The relatively small data base available and the minimal published information available also can contribute to making the physician and patient populations particularly vulnerable under accelerated approval circumstances.

Reliance on court actions (such as seizures, injunctions, and criminal prosecutions) can be effective in ending false promotions, but can only be initiated after the fact, when harm has already occurred. Corrective efforts can

be helpful but are always somewhat delayed. Under the circumstances of accelerated approval, FDA believes that it is far preferable to avoid problems by reviewing the promotional materials in advance of drug approval and of dissemination of the materials.

17. Two comments supported the provision about submission of promotional materials. One comment urged the agency to require that specific patient information be included in promotional materials to indicate the fact that the drug's clinical benefit has not yet been established. For drugs approved under the restricted use provision, the comment recommended that the labeling specify in detail the exact restrictions placed on the drug. In both cases, the comment recommended that this patient information appear as boxed warnings.

Section 502(n) of the act and regulations at § 202.1(e)(1) (21 CFR 202.1(e)(1)) require prescription drug advertisements (promotional material) to contain, among other things, a true statement of information in brief summary relating to side effects, contraindications, and effectiveness, which would include warnings, precautions, and limitations on use. The information in brief summary relating to side effects, contraindications, and effectiveness is required to be based solely on the approved labeling. Therefore, to the extent that a drug's labeling reflects the extent of clinical exposure and includes appropriate warnings, a drug's promotional material would also include this information.

FDA regulations governing prescription drug labeling (21 CFR 201.56 and 201.57) require that serious adverse reactions and potential safety hazards, as well as limitations in use imposed by them, be included in the "Warning" section of the labeling. In the case of approval based upon effect on a surrogate endpoint, the "Indications and Usage" section of the labeling would reflect the nature of the demonstrated effect. If the approval is based on use restrictions, the label would also specify the restrictions.

FDA may require boxed warnings if there are special problems associated with a drug, particularly those that may lead to death or serious injury (21 CFR 201.57(e)). The agency does not agree that information related to clinical benefit or use restrictions for accelerated approval drugs would necessarily always require a boxed warning.

As indicated by §§ 314.550 and 601.45 of the final rule, applicants will be required to submit promotional materials prior to approval and in advance of dissemination subsequent to approval whether the product is a new drug, an antibiotic, or a biological product.

18. One comment contended that FDA review and approval of all promotional pieces before their use will indefinitely delay product marketing campaigns and other patient and physician educational activities, which are essential to market a product, thereby significantly diminishing the advantage of securing an early approval for the applicant. The comment further contended that the requirement to submit "all promotional materials * * * intended for dissemination or publication upon marketing approval" will be overly burdensome for FDA and will unnecessarily slow down the process for review of all materials, not just those for products subject to this proposed rule. The comment recommended that FDA only request for review the primary advertising pieces, such as the introductory letter to physicians, the main detail piece, and the main journal advertisement, but not the secondary materials, e.g., a letter to pharmacists, of the initial promotional campaign.

As previously discussed in this preamble, FDA will be reviewing an applicant's planned promotional materials both prior to approval of an application (reflecting the initial campaign) and subsequent to approval to ascertain whether the materials might adversely affect the drug's sensitive risk/benefit balance. Because all promotional materials, including those referred to by the comment as "secondary" materials, can have significant adverse effects if they are misleading, the agency does not agree that such materials should, as a matter of course, not be requested for review. Insofar as such materials may be directly derived from the introductory letter to physicians, or other materials characterized by the comment as "primary" materials, the additional time to review the derivative materials should not be extensive.

The agency does not agree with the comment's contention that the requirement to submit all promotional materials prior to and subsequent to approval will indefinitely delay marketing campaigns and educational activities or be overly burdensome to FDA reviewers. FDA is committed to rapid review and evaluation of all drugs considered for approval under this rule and will promptly review the promotional materials.

19. One comment suggested a passive, time-limited clearance system for review of advertising after the initial promotional campaign such as that used for review of IND's, which would allow the sponsor to proceed to use promotional materials after an allotted timeframe, such as 30 days, unless otherwise notified by FDA.

As indicated by this comment and others, additional clarification regarding both timing and content of the submissions of promotional materials seems useful. Therefore, the agency is revising proposed §§ 314.550 and 601.45 to make it clear that, unless otherwise informed by the agency, applicants must submit during the preapproval review period copies of all promotional materials intended for dissemination or publication within the first 120 days following marketing approval. The initial promotional campaign, sometimes referred to as the "launch campaign," often has a significant effect on the climate of use for a new product. As discussed elsewhere in this preamble, the risk/benefit balance of accelerated approval products is especially sensitive, and inappropriate promotion may adversely affect the balance with resulting harm.

There may be some instances in which promotional materials that had not been completed and submitted by the applicant prior to approval would be beneficial in fostering safe and effective use of the product during the first 120 days. Under revised §§ 314.550 and 601.45, FDA would have the discretion to consider such materials at a later time. An applicant who requested permission to include additional materials among those disseminated within the first 120 days following product approval would be notified of FDA's determination. If FDA agreed that dissemination of such materials was acceptable, the materials could then be disseminated or published upon notification.

For promotional materials intended for dissemination subsequent to the initial 120 days under §§ 314.550 and 601.45 FDA would review the submitted materials within 30 days of receipt. This 30-day period is meant to be time-limited, so that the applicant will be assured of no unnecessary delay. It will be important for the applicant to identify the materials being submitted appropriately, so that it is clear that the materials are subject to the 30-day review period. The agency intends to review all such materials promptly, and to notify the applicant of any identified problems as soon as possible. The agency expects that, if the agency notifies the applicant of significant objections to the proposed materials, no materials will be disseminated or published until the agency's objections are resolved. The applicant should plan to allow sufficient time after receiving

FDA's comments for resolving differences and incorporating requested changes in the submitted materials prior to dissemination or publication.

When FDA removes the requirement for advance submission of promotional material, the agency will continue to offer a prompt review of all voluntarily submitted promotional material.

E. Postmarketing Restrictions

FDA received many comments on the proposed requirement to limit distribution to certain facilities or physicians with special training or experience, or condition distribution on the performance of specified medical procedures if such restrictions are needed to counterbalance the drug's known safety concerns.

20. Several comments questioned FDA's authority to impose restrictions on distribution or use after an approved drug is marketed. Two comments disagreed with the statutory provisions cited by FDA in the proposed rule as its authority to impose restrictions on distribution or use stating that they refer only to FDA's general authority to ensure that drugs are not misbranded, which is an entirely separate issue. Another comment argued that section 503(b) of the act (21 U.S.C. 353(b)) contemplates that the issues warranting a restriction as to distribution are not factors in whether a drug product is "safe" for purposes of approval, but rather only whether the product must be limited to prescription status. Two comments said that, in the absence of specific statutory authority, the courts clearly have refused to permit FDA to impose restrictions on distribution and cited *American Pharmaceutical Association (APhA)* v. *Weinberger*, 377 F. Supp. 824, 829 n. 9 (D.D.C. 1974), *aff'd sub nom. APhA* v. *Mathews*, 530 F.2d 1054 (D.C. Cir 1976), a case concerning conditions placed on the approval of the drug methadone.

Some comments asserted that placing restrictions on the distribution of an approved drug to only certain facilities or physicians, or restricting use to certain medical procedures interferes with the practices of medicine and pharmacy, which the comments contended FDA does not have the authority to regulate.

The agency believes that the restrictions to ensure safe use contemplated for approvals under §§ 314.520 and 601.42 are authorized by statute. As discussed in the preamble to the proposed rule (57 FR 13234 at 13237), sections 501, 502, 503, 505, and 701 of the act provide broad authority for FDA to issue regulations to help assure the safety and effectiveness of new drugs.

The agency does not agree with the comments' contention that the misbranding provisions of the act are irrelevant. Section 502(a) of the act prohibits false or misleading labeling of drugs, including (under section 201(n) of the act) failure to reveal material facts relating to potential consequences under customary conditions of use. Section 502(f) of the act requires drugs to have adequate directions for use and adequate warnings against unsafe use, such as methods of administration, that may be necessary to protect users. In addition, section 502(j) of the act prohibits use of drugs that are dangerous to health when used in the manner suggested in their labeling. Each of these misbranding provisions is intended, at least in significant part, to protect consumers against the marketing of drugs that would not be safe under certain conditions of use. Section 701(a) of the act authorizes FDA to issue regulations for the efficient enforcement of the act. The restrictions on use contemplated by §§ 314.520 and 601.42 help to ensure that products that would be misbranded under section 502 of the act are not marketed.

The restrictions on use imposed under section 503 of the act, which relate to prescription use limitations, primarily concern whether a drug is safe for use except under the supervision of a licensed practitioner. While the agency agrees that the restrictions imposed under §§ 314.520 and 601.42 concerning distribution to certain facilities or physicians with special training or experience would be in addition to ordinary prescription limitation, FDA believes these restrictions are consistent with the spirit of section 503 of the act, as well as the other provisions of the act referred to, in ensuring safe use.

New drugs may be approved under section 505(d) of the act only if they are safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. In addition, for approval, a drug's labeling must not be false or misleading based on a fair evaluation of all material facts, which would include details about the conditions of use. For biological products, section 351(d) of the PHS Act also authorizes the imposition of restrictions through regulations "designed to insure the continued safety, purity, and potency" of the products.

The agency disagrees with the comments' implication that the courts' rulings in *American Pharmaceutical Association (APhA)* v. *Weinberger* mean there is no statutory authority to impose restrictions on distribution for accelerated approval drugs. The situation considered in that case is readily distinguishable from the situation addressed in §§ 314.520 and 601.42 of the accelerated approval regulations. The *APhA* case concerned a regulation that withdrew approval of NDA's for methadone, but permitted distribution to certain maintenance treatment programs and certain hospital and community pharmacies. Because methadone is a controlled substance within the provisions of the Controlled Substances Act, which is implemented by the Drug Enforcement Administration with the Justice Department, the district court concluded that the question of permissible distribution of the drug was within the jurisdiction of the Justice Department, not FDA. The Court of Appeals determined that the type of misuse associated with methadone, i.e., misuse by persons who have no intent to try to use drugs for medical purposes, differed from safety issues contemplated for control under section 505 of the act. In contrast, the restrictions contemplated under §§ 314.520 and 601.42 are precisely those deemed necessary to ensure that section 505 criteria have been met, i.e., restrictions to ensure that the drug will be safe under its approved conditions of use. It is clearly FDA's responsibility to implement the statutory provisions regarding new drug approval.

Nor does FDA agree that the provisions placing restrictions on distribution to certain facilities or physicians, or conditioned on the performance of certain medical procedures, impermissibly interfere with the practice of medicine and pharmacy. There is no legal support for the theory that FDA may only approve sponsors' drugs without restriction because physicians or pharmacists may wish to prescribe or dispense drugs in a certain way. The restrictions under these provisions would be imposed on the sponsor only as necessary for safe use under the extraordinary circumstances of the particular drug and use. Without such restrictions, the drugs would not meet the statutory criteria, could not be approved for distribution, and would not be available for prescribing or dispensing. The agency, as a matter of longstanding policy, does not wish to interfere with the appropriate practice of medicine or pharmacy. In this instance, the agency believes that rather than interfering with physician or pharmacy practice, the regulations permit, in exceptional cases,

approval of drugs with restrictions so that the drugs may be available for prescribing or dispensing.

21. One comment asserted that postmarketing restrictions on distribution to certain facilities or physicians with certain training or experience should be limited to rare occasions in cases of extreme hazard to patient safety in which toxicity of a particular drug may require it, but should not be applied because of insufficient efficacy data. Some comments argued that safety issues in the context of drug use should be addressed through patient management and effective product labeling, not through restricted distribution. In support of this argument, the comments cited the labeling of oncologic drugs, which provides physicians with adequate warnings and recommendations for their use without limiting distribution.

FDA agrees with these comments in part and intends to impose restrictions on distribution or use under this rule only in those rare instances in which the agency believes carefully worded labeling for a product granted accelerated approval will not assure the product's safe use. As stated in the preamble to the proposed rule (57 FR 13234 at 13237), FDA believes that the safe use of most prescription drugs will continue to be assured through traditional patient management by health professionals and through necessary safety warnings in the drug's labeling.

22. Two comments asked who will determine if restricted distribution should occur and what facilities or physicians with special training or experience will participate. Several comments expressed concern that restricted distribution and/or conditional use may not include all health care professionals who should participate in safe and effective patient care. Two organizations representing pharmacists asked that FDA develop functional and objective criteria that clearly establish the activities of pharmacists, physicians, and others in the care of patients receiving a drug under restricted distribution. The comments asserted that any health care professional that met these criteria should be allowed to participate in distribution of the drug and care of the patient. One comment recommended that any postmarketing restrictions on distribution or use of a drug approved under the accelerated approval process be developed by appropriate FDA advisory committees or panels expanded to include physicians and pharmacists with expertise in the therapeutic area being considered and in relevant drug distribution systems. Where appointment of pharmacists to these committees or panels is not feasible, the comment recommended that FDA use pharmacists in a consultant capacity. Another comment argued that current systems for drug distribution incorporate "checks and balances" such that prescribers and pharmacists work together to assure safe use of a drug by a patient. Two comments would oppose any restricted distribution system that allows manufacturers exclusively to deliver prescription drugs directly to patients. One comment asked whether FDA or the applicant would monitor the criteria for restricted distribution sites or physicians.

The medical reviewing divisions within FDA's CDER and CBER will determine if restricted distribution or use should be imposed. FDA will usually seek the advice of outside expert consultants or advisory committees before making this determination, and will, of course, consult with the applicant.

The agency does not agree that FDA should develop criteria that clearly establish the activities of health care professionals in the care of patients receiving a drug approved under this rule and for which restricted distribution has been imposed. Any postmarketing restrictions required under this rule will impose an obligation on the applicant to ensure that the drug or biological product is distributed only to the specified facilities or physicians. FDA will seek the advice of outside consultants with expertise in distribution systems or advisory committees when necessary in determining the need for or type of restricted distribution. The limitations on distribution or use imposed under this rule, including specific distribution systems to be used and the applicant's plan for monitoring compliance with the limitations, will have been agreed to by the applicant at the time of approval. The burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed. As appropriate, FDA may monitor the sponsor's compliance with the specified terms of the approval and with the sponsor's obligations.

23. One comment recommended that proposed § 314.520 be modified to include therapeutic outcomes monitoring as a third example of a permissible postmarketing restriction. The comment defined therapeutic outcomes monitoring as the systematic and continual monitoring of the clinical and psychosocial effects of drug therapy on a patient which achieves the objective of preventing problems with drug therapy. Some comments argued that through therapeutic outcomes monitoring, a physician, a pharmacist, and a patient can work together to prevent problems with drug therapy by being constantly alert to signs of trouble. One comment said that indicator data can be routinely reported to a central collection point for utilization review by health care professionals, followed by educational programs to further improve the efficacy of drug therapy.

The postmarketing restrictions set forth in the proposal and in this final rule are intended to enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restriction. Therapeutic outcomes monitoring does not contribute to that enhancement, and would not be required under this rule.

24. Some comments asked that FDA clarify how products will move from restrictive status to a regular prescription drug status. The comments asserted that all conditions associated with accelerated approval should automatically terminate following completion of confirmatory clinical trials; one comment urged FDA to explicitly state this in the final rule. One comment asserted that restrictions should automatically be removed 180 days after a supplemental application containing the data from the postmarketing study has been filed if FDA has not yet acted upon the supplemental application and the product should be deemed approved as if by "traditional" procedures and all other provisions of the act should apply, e.g., the applicant must have a formal hearing before removal of the product from the market.

FDA will notify the applicant when a particular restriction is no longer necessary for safe use of the product. In the case of drugs approved with a requirement for postapproval studies, FDA would expect that all of the postapproval requirements set forth in this rule, i.e., submission of promotional material and use of expedited withdrawal procedures, would no longer apply after postmarketing studies have verified and described the drug's clinical benefit. Concurrent with the review of the postmarketing studies, if requested, FDA will also review the need to continue any restrictions on distribution that have been imposed. In the case where restrictions on distribution or use have been imposed, such restrictions would be eliminated only if FDA determines that safe use of the product can be assured without them, through appropriate labeling. In

some cases, however, that assurance could not be expected and the nature of the specific safety issue raised by the product might require continued restrictions. FDA has added new §§ 314.560 and 601.46 to state when postapproval requirements will no longer apply and state that the applicant may petition the agency, in accordance with 21 CFR 10.30, at any time to remove specific postapproval requirements.

With respect to the suggested time period for removing restrictions on distribution or use following submission of a supplemental application containing the data from a postmarketing study, FDA does not believe it should prescribe any specific time period. These applications will receive a priority rating and FDA is firmly committed to expedited review of an application considered for accelerated approval and all data submitted from a postmarketing study to verify clinical benefit and believes most reviews will be completed and action taken within 180 days.

25. One comment argued that, as proposed, it is not clear how accelerated approval would apply to drugs which fall under the conditions described in §§ 314.520 and 601.42, which state the postmarketing restrictions on distribution or use that FDA may apply, because the language of these sections explicitly states that the sections apply to products "shown to be effective," which are already adequately covered by the act. To the comment, the language "shown to be effective" implies that full Phase 3 efficacy trials have been conducted, assessed, and deemed to demonstrate that the drug is effective for its proposed use. If the clinical data demonstrate that the product has an acceptable safety profile, the safe use of the drug should be addressed in the product labeling. Thus, the comment argued that §§ 314.520 and 601.42 should not be included in new subpart H of part 314 and subpart E of part 601, respectively, which deal with accelerated approval because these sections explicitly apply to products shown to be effective under a full drug development program.

Sections 314.520 and 601.42 apply not only to drugs and biological products approved on the basis of an effect on a surrogate endpoint but also to drugs and biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses using clinical endpoints and that have serious toxicity. In either case, if the products are so potentially harmful that their safe use cannot be assured through carefully worded labeling, FDA will approve the products for early marketing only if postmarketing restrictions on distribution or use are imposed. The phrase "shown to be effective" was not intended to distinguish drugs approved under new subpart H from drugs approved under any other subpart of the regulations. All drugs approved will have had effectiveness demonstrated on the basis of adequate and well-controlled studies, whether the endpoint of the studies is a surrogate endpoint or a clinical endpoint.

26. One comment expressed concern that the proposed restricted distribution or use provisions would restrict or eliminate the wholesale distribution of drugs approved through the accelerated approval process.

The limitations on distribution or use required under this rule are imposed on the applicant. Therefore, the burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed. This rule does not specify how a manufacturer will distribute its product to those receiving the product under the approval terms. FDA will only determine which facilities or physicians may receive the drug, and the applicant will have agreed to this limitation on distribution or use.

27. One comment expressed concern that the proposed postmarketing restriction provision does not preclude a physician to whom restricted distribution applies from prescribing drugs approved under the accelerated approval process for unapproved (off-label) uses.

The comment is correct that this rule does not itself prevent a physician from prescribing a drug granted accelerated approval for an unapproved use. Under the act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and that FDA has approved. Physicians may choose to prescribe the drug for a condition not recommended in labeling. Such off-label use would, of course, be carried out under the restrictions imposed under this section. FDA also believes that physicians will be cognizant of the product's special risks and will use such drugs with particular care. The labeling of products approved under this rule will include all necessary warnings and full disclosure labeling would generally reflect the extent of clinical exposure to the drug.

F. Postmarketing Studies

28. Three comments argued that FDA does not have the authority to require postmarketing studies to be performed as a condition of approval based on a "surrogate" endpoint. One comment stated that it is widely accepted that the act empowered the agency to define the type and extent of efficacy data necessary to approve a product application. If a surrogate marker can be shown to be sufficiently related to actual patient benefit, then, the comment asserted, data regarding the effect of a drug on a surrogate marker constitute acceptable proof of efficacy under the act. Two comments urged FDA to continue to ask applicants to agree voluntarily to perform postmarketing studies when medically warranted as is the current policy under the traditional approval process. One comment expressed concern that requiring postmarketing studies may become the norm rather than the exception.

The agency's response to comment 1. explained the circumstances in which FDA might conclude that a drug should be marketed on the basis of an effect on a surrogate endpoint reasonably likely to predict clinical benefit only if studies were carried out to confirm the presence of the likely benefit. As discussed in the preamble to the proposed rule (57 FR 13234 at 13236), FDA believes that it is authorized by law to require postmarketing studies for new drugs and biological products. Section 505(d) of the act provides for the approval of new drugs for marketing if they meet the safety and effectiveness criteria set forth in section 505(d) of the act and the implementing regulations (21 CFR part 314). As discussed in the proposed rule, to demonstrate effectiveness, the law requires evidence from adequate and well-controlled clinical studies on the basis of which qualified experts could fairly and responsibly conclude that the drug has the effect it is purported to have. Under section 505(e) of the act, approval of a new drug application is to be withdrawn if new information shows that the drug has not been demonstrated to be either safe or effective. Approval may also be withdrawn if new information shows that the drug's labeling is false or misleading.

Section 505(k) of the act authorizes the agency to promulgate regulations requiring applicants to make records and reports of data or other information that are necessary to enable the agency to determine whether there is reason to withdraw approval of an NDA. The agency believes that the referenced reports can include additional studies to evaluate the clinical effect of a drug approved on the basis of an effect on a surrogate endpoint. Section 701(a) of the act generally authorizes FDA to issue

regulations for the "efficient enforcement" of the act.

With respect to biological products, section 351 of the PHS Act provides legal authority for the agency to require postmarketing studies for these products. Licenses for biological products are to be issued only upon a showing that they meet standards "designed to insure the continued safety, purity, and potency of such products" prescribed in regulations (42 U.S.C. 262(d)). The "potency" of a biological product includes its effectiveness (21 CFR 600.3(s)).

The agency notes that it has in the past required postmarketing studies as a prerequisite for approval for some drugs (see 37 FR 201, January 7, 1972; and 37 FR 26790, December 15, 1972).

29. One comment recommended that FDA require that specific timelines for completion of the required postmarketing studies be included in the marketing application. The comment further suggested that, if the sponsor fails to meet its timelines, approval of its application be withdrawn, or in the event it is difficult to withdraw approval of drugs for serious or life-threatening diseases, FDA should establish substantial fines and penalties for sponsors that deliberately withhold information from FDA regarding the preliminary results and the progress of their postmarketing studies, or delay the completion of such studies. The comment also urged FDA to publish in the **Federal Register** identification of manufacturers who are not meeting their obligation to complete the required postmarketing studies on time. These recommendations were prompted by the comment's concern that once a manufacturer is granted approval for its product, the manufacturer will have little incentive to complete postmarketing studies in a timely manner, especially if the preliminary results of such studies indicate that the drug may not be safe and/or effective. Another comment urged FDA to include in the final rule language that requires the participation of pharmacists in postmarketing studies because pharmacists can serve as an additional source of information on therapeutic outcomes of patients taking drugs approved under this rule and monitoring for such drugs.

The agency expects that the requirement for postmarketing studies will usually be met by studies already underway at the time of approval and that there will be reasonable enthusiasm for resolving the questions posed by those studies. The plan for timely completion of the required postmarketing studies will be included in the applicant's marketing application. In addition, in accord with the annual reporting requirements at § 314.81(b)(2)(vii) (21 CFR 314.81(b)(2)(vii), an NDA applicant is required to provide FDA with a statement of the current status of any postmarketing studies. FDA declines to impose the sanctions suggested by the comment for failure of an applicant to meet its plans for completion of a postmarketing study. FDA believes this rule applies appropriate regulatory sanctions. Under the proposed rule and this final rule, FDA may withdraw approval of an application if the applicant fails to perform the required postmarketing study with due diligence.

FDA believes that it is not within the scope of this rule to establish the role of pharmacists in postmarketing studies. That role should more properly be defined by the clinical investigator and each institution or facility at which a postmarketing study is conducted.

30. One comment asserted that the proposal sets forth an inherent contradiction between the way FDA evaluates the benefit and risk for drugs today and the way the proposal contemplates. The comment argued that now, if postmarketing data raise questions about the risk associated with a drug product, FDA considers that data along with the other data known about the product, and determines whether, based on the overall knowledge about the drug, there is a need to seek withdrawal of approval. Under this proposal, if the postmarketing study data raised questions about the risk of the product, FDA would seek withdrawal of approval, whether or not the new data really made a fundamental difference to what is known about the benefit and risk of the product.

FDA does not agree that the contradiction described by the comment exists. Under the circumstances of accelerated approval, approval would be based on a weighing of the benefit suggested by the effect on the surrogate endpoint against known and potential risks of the drug. Should well-designed postapproval studies fail to demonstrate the expected clinical benefit, the benefit expected at the time of approval (reasonably likely to exist) would no longer be expected and the totality of the data, showing no clinical benefit, would no longer support approval. This evaluation of the data is not different from considerations that would apply in evaluating data in the case of a drug approved under other provisions of the regulations.

31. Two comments expressed the view that the proposed requirement for postmarketing studies may raise important ethical questions because once a drug product is approved, it may be unethical, depending on the circumstances, for a physician to conduct a study using a placebo control. One comment also contended that a postmarketing study requirement could compromise the NDA holder's ability to enroll sufficient numbers of patients in the study when the new approved drug and possible alternative therapies are widely available to patients.

Usually, and preferably, because of problems suggested in the comment, the requirement for postmarketing studies will be met by studies already underway at the time of approval, e.g., by completion of studies that showed an effect on the surrogate. FDA recognizes that ethical considerations will play a central role in the type of study carried out, a choice that will depend upon the type and seriousness of the disease being treated, availability of alternative therapies, and the nature of the drug and the patient population. There often are alternatives to use of a placebo control, including active control designs and dose-response studies that can satisfy both the demands of ethics and adequacy of design.

32. One comment contended that the term "postmarketing study" is used inconsistently in the proposed rule. The comment argued that "postmarketing study" is an accepted regulatory term of art which, to this point, has referred to studies conducted to confirm safety (not efficacy), after an approval has been granted, whereas in this proposal, a "postmarketing study" refers to a study required to establish clinical efficacy (i.e., a Phase 3 study), but not necessarily safety, although safety data will be collected. To prevent confusion and to differentiate between these required postmarketing confirmatory efficacy studies and safety studies traditionally conducted after approval and to clarify that products granted accelerated approval have been approved on the basis of Phase 2 (surrogate endpoint) data, the comment suggested changing the term "postmarketing study" to "Phase 3 study" in this rule except where traditional postmarketing studies are intended. The comment also suggested that the term "Phase 3 study" be defined as a study required to confirm findings of efficacy based upon surrogate data collected in Phase 2, which will be conducted after an accelerated approval has been granted and will be required before restrictions set forth in § 314.520 are removed.

The agency does not believe that the comment has accurately described accepted meanings of various terms.

The term postmarketing study does not refer to any particular kind of study, but to studies carried out after a drug is marketed, often as part of an agreement by a sponsor to do so. These have included pharmacokinetic, drug-drug interaction, and pediatric studies, studies of dose-response or of higher doses, and studies of new uses. The term is not limited to safety studies. Moreover, Phase 2 and 3 studies are not distinguished by the endpoints chosen. Phase 3 hypertension studies, for example, still measure blood pressure, not stroke rate. The agency believes that the use of the "postmarketing study" in the final rule is appropriate and consistent.

G. Withdrawal of Approval

33. One comment supported the proposed withdrawal of approval procedure. Other comments asserted that the proposed procedure does not provide the applicant with the procedural safeguard of a formal evidentiary hearing guaranteed by section 505 of the act and the Administrative Procedure Act (APA). As an example, the comments said that based on a finding of a single study failing to show clinical benefit or misuse of any promotional material, an approved new drug would be subject to withdrawal from the market with only a minimal opportunity for the NDA holder to be heard. The comments argued that section 505(e) of the act guarantees applicants "due notice and opportunity for a hearing" on withdrawal of an NDA in compliance with APA hearing standards, thus FDA must conduct hearings on withdrawals of NDA's using the formal adjudicatory procedures of the APA. One comment asserted that, under the proposed procedure, there is the absence of a discernible legal standard, an inability to cross-examine, the prosecuting attorney and judge are one and the same person, and there is a lack of even minimal formal evidentiary procedures. The comment expressed doubt that the proposed procedure would be sufficient to create a record suitable for review by a Court of Appeals, which must be able, on the basis of such a record, to determine whether the approval is supported by "substantial evidence."

FDA believes the withdrawal procedures set forth in proposed §§ 314.530 and 601.43 and in this final rule are consistent with relevant statutes and provide applicants adequate due process. As stated in the proposed rule, in issuing its general procedural regulations, FDA decided to afford NDA holders an opportunity for a formal evidentiary hearing even though the courts had not decided that such a hearing was necessarily legally required (see 40 FR 40682 at 40691, September 3, 1975). In promulgating its procedural regulations, FDA also determined that a formal evidentiary hearing is not required before withdrawing approval of biological products, but that it would be appropriate to apply the same procedures to biological products as to drug removal (see 40 FR 40682 at 40691).

Through the hearing process in this final rule, as in the proposed rule, applicants will be afforded the opportunity to present any data and information they believe to be relevant to the continued marketing of their product. The proposed process also would have permitted the presiding officer, the advisory committee members, a representative of the applicant, and a representative of the Center that initiates the withdrawal proceedings to question any person during or at the conclusion of the person's presentation. As discussed below in response to a comment, FDA has decided to allow up to three representatives of the applicant and of the Center to question presenters. Participants could comment on or rebut information and views presented by others. As with ordinary 21 CFR part 15 hearings, the hearing will be transcribed. Subsequent to the hearing, the Commissioner of Food and Drugs would render a final decision on the matter. The agency believes that the administrative record created through this process would be sufficient for judicial review.

The agency emphasizes that, as part of the approval process under this rule, applicants will have agreed that these withdrawal procedures apply to the drug for which they seek approval; applicants objecting to these procedures may forego approval under these regulations and seek approval under the traditional approval process. Under such circumstances, applicants would not have the benefit of accelerated approval; if the drug were subsequently approved, however, before withdrawal of the approval, the applicant would have an opportunity for a 21 CFR part 12 hearing.

34. One comment noted that the "imminent hazard" provision of section 505(e) of the act allows FDA to suspend approval of a product, immediately, if it is found to pose an imminent hazard to the public health. As an alternative to the proposed withdrawal procedure or in addition to the "imminent hazard" statutory provision, the comment suggested that, when confronted with a dangerous product on the market, FDA could request that the applicant voluntarily withdraw its product, and most applicants would comply if a legitimate hazard exists.

As noted in the proposed rule, FDA and applicants have often reached mutual agreement on the need to remove a drug from the market rapidly when significant safety problems have been discovered. However, applicants usually have been unwilling to enter into such agreements when doubts about effectiveness have arisen, such as following the review of effectiveness of pre-1962 approvals carried out under the Drug Efficacy Study Implementation (DESI) program. For drugs approved under the accelerated procedure regulations, the risk/benefit assessment is dependent upon the likelihood that the surrogate endpoint will correlate with clinical benefit or that postmarketing restrictions will enable safe use. If the effect on the surrogate does not translate into a clinical benefit, or if restrictions do not lead to safe use, the risk/benefit assessment for these drugs changes significantly. FDA believes that if that occurs, rapid withdrawal of approval as set forth in this rule is important to the public health.

35. Under the proposed withdrawal procedures, in addition to other persons, one representative of the Center that initiates the withdrawal proceedings may question participants at a withdrawal of approval hearing. One comment objected to limiting the Center to one representative because detailed knowledge about a drug product is likely to be available from several scientists.

The proposed limitation of questioning to single representatives of the initiating Center and the applicant was intended to make the proceedings manageable. On further consideration, the agency has determined that it would be appropriate and manageable to allow up to three persons to be designated as questioners for the applicant and for FDA. Sections 314.530(e)(2) and 601.43(e)(2) have been revised accordingly.

36. Some comments questioned FDA's ability to withdraw approval under the proposed procedures efficiently or effectively because of: (1) The lack of assurance that the results of postmarketing studies will be promptly provided to FDA; (2) limited agency resources to review study results and act upon them promptly; (3) the difficulties associated with establishing that an approved drug is "ineffective;" and (4) political pressure not to rescind the approval of NDA's for drug products that may lack evidence of effectiveness,

especially if no clearly effective alternative treatments are available. One comment offered the opinion that where a drug shows only modest evidence of benefit, perhaps on a surrogate endpoint, and only shows equivocal evidence of clinical efficacy in postmarketing studies it would be difficult and socially disruptive to withdraw approval and remove the drug from the market if the drug has become well established and accepted, and there is no issue of toxicity. Another comment believed it would be difficult to withdraw approval of a drug that may be beneficial in a subpopulation but which, in fact, has not been shown to be efficacious in broader patient population studies. The comments suggested the need for a lesser sanction.

Another comment suggested that expediting removal of a product from the market could be accomplished by using a procedure like the "imminent hazard" provision of the act, i.e., immediate removal of the drug from the market if any of the conditions listed in proposed § 314.530 were met followed by a hearing.

Although the potential difficulties cited by the comments are real, they are not fundamentally different from determinations FDA regularly must make in carrying out its responsibilities. The new regulations provide for an expedited procedure to withdraw approval; they do not guarantee that results of studies will be wholly unambiguous or that FDA will always be able to prevail in its view as to the need for withdrawal, any more than current withdrawal procedures do. The studies being carried out under these provisions will be conspicuous and important and their completion will be widely known. There is no reason to believe their results would or could be long hidden. A study that fails to show clinical effectiveness does not prove a drug has no clinical effect but it is a study that, under § 314.530, will lead to a withdrawal procedure because it has failed to show that the surrogate endpoint on which approval was based can be correlated with a favorable clinical effect. This may have occurred because the study was poorly designed or conducted; while FDA will make every effort to avoid this, the commercial sponsor has the responsibility for providing the needed evidence confirming clinical benefit. As previously discussed, §§ 314.510 and 601.41 have been revised to clarify that required postmarketing studies must also be adequate and well-controlled. The possibility that an ineffective drug has become "accepted" is not a basis for continued marketing. FDA intends to implement the provisions of § 314.530 as appropriate; data that are ambiguous will inevitably lead to difficult judgments.

A drug with clear clinical effectiveness in a subset of the population, but not in the population described in labeling, would have its labeling revised to reflect the data. Withdrawal would be inappropriate under such circumstances.

If an imminent hazard to the public health exists, the Secretary of Health and Human Services may suspend approval of an application and then afford the applicant an opportunity for an expedited hearing. In the absence of a significant hazard requiring immediate withdrawal, FDA believes the expedited procedure described in the rule satisfies the need for prompt action while, at the same time, allowing opportunity for discussion and debate before withdrawal.

37. One comment noted that the proposed rule would allow FDA to withdraw approval for failure to perform the required postmarketing studies with due diligence. The comment asserted that the act does not permit FDA to withdraw approval on this ground. Another comment, however, suggested that because proposed §§ 314.530 and 601.43 cite grounds for withdrawal of approval that are not grounds under the act, the language of these proposed sections should be revised to use language that closer aligns to that used in the act, e.g., describe a "postmarketing study" in statutory language.

FDA reaffirms the position expressed in the preamble to the proposal (57 FR 13234 at 13239) that there is adequate authority under the act to withdraw approval of an application for the reasons stated under proposed §§ 314.530 and 601.43, which include failure of an applicant to perform the required postmarketing study with due diligence. Section 505(e) of the act authorizes the agency to withdraw approval of an NDA if new information shows that the drug has not been demonstrated to be either safe or effective. Approval may also be withdrawn if the applicant has failed to maintain required records or make required reports. In addition, approval may be withdrawn if new information, along with the information considered when the application was approved, shows the labeling to be false or misleading.

For biological products, section 351(d) of the PHS Act authorizes approval of license applications under standards designed to ensure continued safety, purity, and potency. "Potency" for biological products includes effectiveness (21 CFR 600.3(s)). The PHS Act does not specify license revocation procedures, except to state that licenses may be suspended and revoked "as prescribed by regulations."

For drugs approved under § 314.510, FDA will have determined that reports of postmarketing studies are critical to the risk/benefit balance needed for approval; if those reports are not forthcoming, then, under authority of section 505(d) of the act, the drug cannot on an ongoing basis meet the standards of safety and efficacy required for marketing under the act. Therefore, it is important to ensure that the applicant make a good faith effort to complete any required postmarketing studies in a timely manner so that FDA can rapidly determine whether the surrogate endpoint upon which the drug was approved has been confirmed to correlate with clinical benefit. Failure to submit the study results in a timely fashion would also constitute failure to make a required report. Similarly, without submission of the information from required postmarketing studies on biological products approved under these procedures, the biological product is not assured of continued safety and effectiveness. The license application may, therefore, appropriately be revoked as described in § 601.43.

FDA does not find the statements of the grounds for withdrawal of approval under §§ 314.530 and 601.43 of this rule inconsistent with statutory language or ambiguous. The agency notes that, in the event none of the grounds for withdrawal specifically listed in § 314.530 or § 601.43 applies, but another ground for withdrawal under section 505 of the act or section 351 of the PHS Act and implementing regulations at 21 CFR 314.150 or 601.5 does apply, the agency will proceed to withdraw approval under traditional procedures.

38. Two comments expressed concern that it may be difficult for the agency to enforce the requirement that postmarketing studies be pursued with due diligence. The comments asked what would happen if a sponsor using due diligence is unable to recruit enough patients, or if the sponsor questions the validity of the data from the required postmarketing study, and would clumsy data management be seen as sufficient reason to rescind approval for a marketed drug? Another comment stated that once a product is approved and, by definition, provides a "meaningful therapeutic benefit over existing therapies," study accrual may drop off dramatically as patients may refuse to receive the "old" therapy or

placebo, or physicians may consider it unethical not to treat all patients with the approved indication with the new drug or biological product. Under these circumstances, the comment expressed the opinion that neither the sponsor nor the product should be penalized, nor should there be a threat to withdraw approval. Based on FDA's past history in postmarketing studies, which one comment characterized as resulting in poorly done studies, studies conducted much later than agreed upon, or not at all, the comment expressed the opinion that the "due diligence" with which applicants are expected to carry out postmarketing studies may be an overly great expectation. One comment asked FDA to give examples of when it may withdraw approval if "other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use" (proposed §§ 314.530(a)(6) and 601.43(a)(6)).

FDA does not agree that it will be difficult to enforce the "due diligence" provision of this rule. The "due diligence" provision was designed to ensure that the applicant makes a good faith effort to conduct a required postmarketing study in a timely manner to confirm the predictive value of the surrogate marker or other indicator. Any requirement for postmarketing studies will have been agreed to by the applicant at the time of approval, and if the study is not conducted in a timely manner as agreed to by the applicant, approval of the applicant's application will be withdrawn. FDA will expect any required postmarketing study to be conducted in consultation with the agency. Therefore, should the applicant encounter problems with subject enrollment in a study or ethical difficulties about the type of study to conduct, FDA expects the applicant to discuss these problems with the agency and reach agreement on their resolution.

Examples of other evidence demonstrating the drug product is not shown to be safe and effective could include further studies of the effect of the drug and the surrogate endpoint that fail to show the effect seen in previous studies, new evidence casting doubt on the validity of the surrogate endpoint as a predictor of clinical benefit, or new evidence of significant toxicity.

39. Some comments objected to withdrawal of approval of a drug product approved under the accelerated approval process because of perceived misconduct by the applicant, such as failure to perform a required postmarketing study with due diligence or use of promotional materials that are false or misleading. The comments argued that the primary purpose of the accelerated approval process is to provide improved treatments to desperately ill patients at the earliest possible time, and withdrawal of approval of the new treatments for reasons not directly related to safety or efficacy undermines the purpose of the proposed rule. Two comments suggested that correction of the promotional material without interruption of access to the drug would be a better approach. Another comment suggested that there may be circumstances where continued access to the drug, if accompanied by informed consent, would be appropriate even if substantial questions arise about a product's safety and effectiveness. One comment urged that anticipated withdrawal of approval be preceded by measures to ensure that patients and their physicians will have an uninterrupted supply until alternative treatment arrangements can be made.

The need for "due diligence" in conducting the agreed to postmarketing studies is discussed in paragraph 37. The reasons for concern about misleading promotional materials are discussed under paragraph 16. With respect to promotional materials, FDA expects that, in most cases, any disagreements between the applicant and FDA will be resolved through discussion and modification of the materials, so that the drug or biological product can continue to be marketed. If, however, FDA concludes that the promotional materials adversely affect the risk/benefit conclusion supporting the drug's marketing, the agency intends to minimize the risk to the public health by removing the product from the market through the withdrawal procedures in this rule.

40. One comment expressed concern that the proposed withdrawal procedure may give the appearance of bias or preconceived notions on the part of the agency because the final decision to withdraw approval of a drug would be made by the Commissioner of Food and Drugs and the intention to withdraw approval of the drug will already have been determined by the agency.

Under the withdrawal provisions of this rule, FDA's CDER or CBER, rather than the Commissioner, will initiate the withdrawal proceedings. The withdrawal process will begin with a letter from CDER or CBER notifying the applicant that the Center proposes to withdraw marketing approval and stating the reasons for the proposed action. Although separation of functions will not apply under the provisions of §§ 314.530 or 601.43, the Commissioner's decision regarding withdrawal would not occur until after the applicant had an opportunity for hearing as described in those sections. The Commissioner would then expect to review the issues with objectivity and fairness having had the benefit of the presentations and discussions at the hearing and of the advisory committee's recommendations.

H. Safeguards for Patient Safety

41. One comment asked if drugs approved under the accelerated approval process will be held to the same standards concerning postmarketing safety as drugs approved by the traditional process.

As discussed in the preamble to the proposed rule, applicants gaining approval for new drugs through the accelerated approval procedures will also be expected to adhere to the agency's longstanding requirements for postmarketing recordkeeping and safety reporting (see 21 CFR 314.80 and 314.81). Information that comes to FDA from the applicant or elsewhere that raises potential safety concerns will be evaluated in the same manner that such information is evaluated for drugs approved under the agency's traditional procedures. If the postmarketing information shows that the risk/benefit assessment is no longer favorable, the agency will act accordingly to remove the drug from the market.

42. One comment urged FDA, if the proposed rule were adopted, to require written informed consent so that patients would know that the drugs with which they were being treated had risks and that the benefits had not been adequately established.

The agency does not agree that patients using drug products approved under the accelerated approval regulations should be asked to provide written informed consent. Drugs approved under these provisions are not considered experimental drugs for their approved uses. Like all approved drugs, drugs approved under these provisions will have both risks and benefits. As previously discussed in this preamble, for drugs approved based on studies showing an effect on a surrogate endpoint, the approved labeling will describe that effect. In addition, the labeling will contain information on known and potential safety hazards and precautionary information. As with all prescription drugs, the physician has the responsibility for appropriately advising the patient regarding the drug being prescribed.

43. One comment asked that FDA require manufacturers to maintain an updated list of names, addresses, and phone numbers of physicians prescribing their products approved

under this rule, and in the case of recall or withdrawal of approval, require manufacturers to contact these physicians and encourage them to notify their patients.

FDA does not believe such a procedure is necessary. Furthermore, maintaining such a registry for drugs prescribed through pharmacies would be very difficult. Agency experience with recalls and product withdrawals indicates that the methods of notification that have been developed for such circumstances are adequate.

44. One comment recommended that FDA require patient package inserts (PPI's) for all drugs granted accelerated approval that would state the specific restrictions placed on a drug product and/or the reason for requiring postmarketing studies. In addition, the comment recommended that FDA require the manufacturer to include an adverse drug reaction "hotline" phone number in the PPI along with an FDA phone number. The PPI should inform the patient to report immediately any adverse drug reaction experienced to his or her doctor, the manufacturer, and FDA, and the manufacturer should be required to contact FDA immediately after receiving a report of a serious adverse reaction.

FDA concludes that patient package inserts are not routinely needed for drugs granted accelerated approval, although if circumstances made one appropriate, one would be developed for a particular drug. As with any prescription drug, the approved labeling for a product granted accelerated approval will contain information about the safe and effective use of the product, including all necessary warnings and the extent of clinical exposure. In addition, the conditions of use will be carefully worded to reflect the nature of the data supporting the product's approval. Physicians have the responsibility to inform patients about the safe and effective use of an approved product. Labeling includes suggestions to the physician concerning information to be provided to patients.

The agency notes that in this final rule limited editorial changes have been made to the wording of the proposed rule. The agency has determined that these changes do not affect the intent of the proposed rule.

V. Economic Impact

In accordance with Executive Order 12291, FDA has carefully analyzed the economic effects of this final rule and has determined that it is not a major rule as defined by the Order. Indeed, because firms will not be forced to use the accelerated approval mechanism, applicants will most probably choose to take advantage of the program only where its use is expected to reduce net costs, Similarly, the final rule does not impose a significant economic impact on a substantial number of small entities so as to require a regulatory flexibility analysis under the requirements of the Regulatory Flexibility Act of 1980.

VI. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Paperwork Reduction Act of 1980

This rule does not contain new collection of information requirements. Section 314.540 does refer to regulations that contain collection of information requirements that were previously submitted for review to the Director of the Office of Management and Budget (OMB) under section 3504 of the Paperwork Reduction Act of 1980 (Adverse Drug Experience Reporting, OMB No. 0190–0230).

List of Subjects

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 314 and 601 are amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 376).

2. Subpart H consisting of §§ 314.500 through 314.560 is added to read as follows:

Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

Sec.

Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

§ 314.500 Scope.

This subpart applies to certain new drug and antibiotic products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

§ 314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§ 314.520 Approval with restrictions to assure safe use.

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

§ 314.530 Withdrawal procedures.

(a) For new drugs and antibiotics approved under §§ 314.510 and 314.520, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;

(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Drug Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 314.510 or § 314.520. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the Federal Register in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

§ 314.540 Postmarketing safety reporting.

Drug products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved drug products, as provided in §§ 314.80 and 314.81.

§ 314.550 Promotional materials.

For drug products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 314.560 Termination of requirements.

If FDA determines after approval that the requirements established in § 314.520, § 314.530, or § 314.550 are no longer necessary for the safe and effective use of a drug product, it will so notify the applicant. Ordinarily, for drug products approved under § 314.510, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the drug product's clinical benefit and the drug product would be appropriate for approval under traditional procedures. For drug products approved under § 314.520, the restrictions would no longer apply when FDA determines that safe use of the drug product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30.

PART 601—LICENSING

3. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 513–516, 518–520, 701, 704, 708, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 376, 381); secs. 215, 301, 351, 352 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461).

4. Subpart E consisting of §§ 601.40 through 601.46 is added to read as follows:

Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

Sec.

Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

§ 601.40 Scope.

This subpart applies to certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

§ 601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic,

pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§ 601.42 Approval with restrictions to assure safe use.

(a) If FDA concludes that a biological product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the biological product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the biological product.

§ 601.43 Withdrawal procedures.

(a) For biological products approved under §§ 601.40 and 601.42, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product;

(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Biologics Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 601.40 or § 601.41. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the Federal Register in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

§ 601.44 Postmarketing safety reporting.

Biological products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.

§ 601.45 Promotional materials.

For biological products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 601.46 Termination of requirements.

If FDA determines after approval that the requirements established in § 601.42, § 601.43, or § 601.45 are no longer necessary for the safe and effective use of a biological product, it will so notify the applicant. Ordinarily, for biological products approved under § 601.41, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the biological product's clinical benefit and the biological product would be appropriate for approval under traditional procedures. For biological products approved under § 601.42, the restrictions would no longer apply when FDA determines that safe use of the biological product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30.

Dated: December 7, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

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